This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

See reverse side for additional information.

Interagency Report Control No. 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

1. REGISTRATION NO. 85-R-0003 **CUSTOMER NO.** 1072

FORM APPROVED OMB NO. 0579-0036

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include Zip Code)*

LOVELACE RESPIRATORY RESEARCH INSTITUTE
2425 RIDGECREST SE
ALBUQUERQUE, NM 87108
(505) 348-9400

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS*(sites)*

See Attached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use APHIS FORM 7023A)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic,analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs	53	58	91	0	~~249~~ 149
5. Cats					
6. Guinea Pigs	1	47			47
7. Hamsters		5	112		117
8. Rabbits	20	184	6	29	219
9. Non-Human Primates	100	27*	145	17	189
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					
Ferrets	6	64			64

*5 non-LRRI NHPs were bled on an approved LRRI protocol with permission of the owners.

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all the exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

DEC - 4 2006

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional official)
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143)

S	NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL *(Type or Print)*	DATE SIGNED
[redacted] (b)(6), (b)(7)c	[redacted] (b)(6), (b)(7)c	11-30-06

AI [illegible] 88), which is obsolete

PART I - HEADQUARTERS

(AUG 91)

DEC - 4 2006

✓

Column E Explanation For Lovelace Respiratory Research Institute
Registration Number 85-R-003 Studies

The institute had five studies with USDA species in Category E in the reporting period 10/1/05 to 9/30/06

Study A
Number and species of animal on Study in Category E: 3 Non-human primates Cynomolgus macaques

This purpose of this protocol was to test the virulence of a virus and develop a model of the disease at this institute. This virus could potentially be used by bioterrorists. Monkeys (3) were challenged with a Select Agent A (LRRI –I) administered intravenously and monitored for 28 days post challenge. The institute will test the efficacy of antiviral agents in future studies and thus needs a model of the disease. The painful part of this study was the infection from the pathogen. It was necessary that this challenge stock of virus be characterized and that the pathology of the disease be followed before undertaking therapeutic studies. The use of anesthetics, analgesics, or tranquilizers could interfere with the study of the natural progression of the disease. The use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. It is likely the use of analgesics would interfere with the accurate measurements of the disease process. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hung, C. Y. et. al. Proc Soc Exp Biol Med 142:106-111-1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al., Brain Behav Immun 3: 129-137, 1989). Also, analgesics including buprenorphine can cause histamine release (Marone, G., et al Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., and Marone, G., Chem Immunol 62: 108-131, 1995) and respiratory depression (Soma, L.R., Ann NY Acad Sci 406: 32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway responses. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al, J Immunol 170: 2269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124, 249-252, 2001) and increase the synthesis and release of IL-10 form human macrophages (Sirois, J., et al, J. Immunol 164:2964-2970, 2000). Clearly, the analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33: 328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide.

Validated endpoints of imminent death do not exist for this disease model so best scientific judgment was used to make a call for euthanasia between observation periods. The FDA requires that vaccines against bioterrorist agents be evaluated in animals since studies in humans would be ethically and morally wrong. This study will support future submissions to the FDA under the "Animal Rule" amendment (21CFR parts 314 subpart I and 601 subpart H). At the end of the study all 3 monkeys were classified as a category E.

Study B
Number and species of animal on Study in Category E: 4 Non-human primates Cynomolgus macaques

Monkeys (12) were challenged with a potential bioterrorist Select Agent A (LRRI –I) administered intravenously and then divided into 3 groups: low dose, high dose, or vehicle control. An antiviral drug at a low dose or high dose or vehicle was given by nasogastric dosing 1 hr later and for 13 more days. Thereafter, the animals were monitored and euthanized on Study Day 29 if not necessary to euthanize sooner. The painful part of this study was the infection from this pathogen. It was necessary that the dose of pathogen cause disease so that pathology/survival of the non-drug treated monkeys could be compared with the drug-treated monkeys. The efficacy of an anti-viral cannot be tested without allowing some animals to develop illness following challenge. This study needed to mimic a real-world scenario of a bioterrorist attack where the majority of humans would not have the benefit of anesthetics, analgesics, or tranquilizers. The use of anesthetics, analgesics, or tranquilizers could interfere with the study of the natural progression of the disease. The use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. It is likely the use of analgesics would interfere with the accurate measurements of the disease process. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hung, C. Y. et. al. Proc Soc Exp Biol Med 142:106-111-1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al., Brain Behav Immun 3: 129-137, 1989). Also, analgesics including buprenorphine can cause histamine release (Marone, G., et al Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., and Marone, G., Chem Immunol 62: 108-131, 1995) and respiratory depression (Soma, L.R., Ann NY Acad Sci 406: 32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway responses. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al, J Immunol 170: 2269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124, 249-252, 2001) and increase the synthesis and release of IL-10 form human macrophages (Sirois, J., et al, J. Immunol 164:2964-2970, 2000). Clearly, the analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33: 328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease

process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide.

This study will support future submissions to the FDA under the "Animal Rule" amendment (21CFR parts 314 subpart I and 601 subpart H). The "Animal Rule" applies when adequate and well controlled clinical studies cannot be ethically conducted and field efficacy studies in humans are not feasible. At the end of the study 4 of 12 animals were classified as Category E and 8 were classified as category C.

Study C
Number and species of animal on Study in Category E: 4 Non-human primates Cynomolgus macaques

The purpose of this study was to determine if an antiserum could prevent or ameliorate infection in monkeys. Monkeys (4) were given an intravenous antiserum against a potential bioterrorist agent and then 1 hour later challenged with a Select Agent A (LRRI –II) via head-only inhalation under Telazol anesthesia. An additional 2 monkeys were given vehicle only and then challenged with the pathogen. The animals were monitored for 14 additional days and then all survivors were euthanized. Those that received vehicle or that did not receive protection from the antiserum were euthanized after the disease progressed and death appeared imminent. The infectious disease was the procedure that produced pain and distress. In order to test the efficacy of the antiserum, it was necessary to show that the agent produced the disease in vehicle-treated animals and to follow the progression of the disease in order to compare the pathology of the treated versus the untreated animals. The use of anesthetics, analgesics, or tranquilizers could interfere with the study of the natural progression of the disease. The use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. It is likely the use of analgesics would interfere with the accurate measurements of the disease process. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hung, C. Y. et. al. Proc Soc Exp Biol Med 142:106-111-1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al., Brain Behav Immun 3: 129-137, 1989). Also, analgesics including buprenorphine can cause histamine release (Marone, G., et al Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., and Marone, G., Chem Immunol 62: 108-131, 1995) and respiratory depression (Soma, L.R., Ann NY Acad Sci 406: 32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway responses. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al, J Immunol 170: 2269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124, 249-252, 2001) and increase the synthesis and release of IL-10 form human macrophages (Sirois, J., et al, J. Immunol

164:2964-2970, 2000). Clearly, the analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33: 328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide.

The efficacy of an antiserum cannot be tested without allowing some animals to develop illness following challenge. This study will support future submissions to the FDA under the "Animal Rule" amendment (21CFR parts 314 subpart I and 601 subpart H). The "Animal Rule" applies when adequate and well controlled clinical studies cannot be ethically conducted and field efficacy studies in humans are not feasible. At the end of the study 4 of 6 animals were classified as Category E and 2 of 6 were classified as Category C.

Study D
Number and species of animal on Study in Category E: 6 Non-human primates Cynomolgus macaques

The purpose of this protocol was to test the efficacy of a vaccine at 2 concentrations and to determine whether an adjuvant enhanced the response. Monkeys (11) were divided into 4 groups and challenged with the vaccine on Study Days 1, 14 and 28: 2 control, 3 low-dose antibody + adjuvant, 3 high-dose antibody + adjuvant, and 3 high dose of antibody without adjuvant. The primates were challenged with a Select Agent A (LRRI-III) on Study Day 40 and monitored for two weeks following the challenge. All survivors were euthanized at the two weeks post-challenge. Those that received vehicle or that did not receive protection from the vaccine were euthanized after the disease progressed and death appeared imminent. The infectious disease was the procedure that produced pain and distress. In order to test the efficacy of the vaccine, it was necessary to show that the agent produced the disease in vehicle-treated animals and to follow the progression of the disease in order to compare the pathology of the treated versus the untreated animals. The use of anesthetics, analgesics, or tranquilizers could interfere with the study of the natural progression of the disease. The use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. It is likely the use of analgesics would interfere with the accurate measurements of the disease process. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hung, C. Y. et. al. Proc Soc Exp Biol Med 142:106-111-1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al., Brain Behav Immun 3: 129-137, 1989). Also, analgesics including buprenorphine can cause histamine release (Marone, G., et al Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., and Marone, G., Chem Immunol 62: 108-131, 1995) and respiratory depression (Soma, L.R., Ann NY Acad Sci 406: 32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and

inflammatory diseases by modulating vascular and airway responses. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al, J Immunol 170: 2269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124, 249-252, 2001) and increase the synthesis and release of IL-10 form human macrophages (Sirois, J., et al, J. Immunol 164:2964-2970, 2000). Clearly, the analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33: 328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide.

The efficacy of a vaccine cannot be tested without allowing some animals to develop illness following challenge. This study will support future submissions to the FDA under the "Animal Rule" amendment (21CFR parts 314 subpart I and 601 subpart H). The "Animal Rule" applies when adequate and well controlled clinical studies cannot be ethically conducted and field efficacy studies in humans are not feasible. At the end of the study 6 of 11 animals were classified as category E and 5 of 11 animals were classified as category C.

Study E
Number and species of animal on Study in Category E: 29 New Zealand White Rabbits

The purpose of this protocol was to test the efficacy of a vaccine against a biological agent that could potentially be used by bioterrorists. Forty rabbits were divided into 4 groups (5 males, 5 females per group) and then were administered vehicle or vaccine plus adjuvant either subcutaneously or by intranasal instillation on Study Days 1, 15 and 29. On Study Day 41, the rabbits were challenged with a Select Agent A (LRRI- II) via inhalation and then monitored for two weeks. At this time, all survivors were euthanized. Those that received vehicle or that did not receive protection from the vaccine were euthanized after the disease progressed and death appeared imminent. In order to test the efficacy of the vaccine, it was necessary to show that the agent produced the disease in vehicle-treated animals and to follow the progression of the disease in order to compare the pathology of the treated versus the untreated animals. The use of anesthetics, analgesics, or tranquilizers could interfere with the study of the natural progression of the disease. The use of analgesics could alter the pathogenic and immunologic response to infection, thus making it impossible to interpret the data obtained in this study. It is likely the use of analgesics would interfere with the accurate measurements of the disease process. Narcotic analgesics were shown to interfere with the mechanism(s) responsible for interferon production (Geher, W.F. et al., J. Toxicol Environ Health 2:577-582, 1977; Hung, C. Y. et. al. Proc Soc Exp Biol Med 142:106-111-1973). Moreover opioids can suppress Natural Killer (NK) cell activity (Beilin, B., et al., Brain Behav Immun 3: 129-

137, 1989). Also, analgesics including buprenorphine can cause histamine release (Marone, G., et al Int Arch Allergy Immunol 124:249-252, 2001; Stellato, C., and Marone, G., Chem Immunol 62: 108-131, 1995) and respiratory depression (Soma, L.R., Ann NY Acad Sci 406: 32-47, 1995). Histamine is a well-known inflammatory mediator and plays a central role in the pathogenesis of allergic and inflammatory diseases by modulating vascular and airway responses. Histamine has been shown to induce activation of human macrophages (Mozzoni, A., et al, J Immunol 170: 2269-2273, 1999), inhibit interferon alpha release from dendritic cells (Marone, G., et al., Int Arch Allergy Immunol, 124, 249-252, 2001) and increase the synthesis and release of IL-10 form human macrophages (Sirois, J., et al, J. Immunol 164:2964-2970, 2000). Clearly, the analgesic-induced release of histamine would directly interfere with the inflammatory process. Studies by Piersman et al, (Lab Anim 33: 328-333, 1999) provide an additional example of how analgesics may modify the expression of the disease process. These investigators, using an established murine model of endotoxemia, showed that the opioids fentanyl and buprenorphine directly altered the outcome of their experiments by modulating the immune response. In this case, both opioids caused significant decreases in circulating levels of tumor necrosis factor alpha following administration of lipopolysaccharide.

The efficacy of a vaccine cannot be tested without allowing some animals to develop illness following challenge. This study will support future submissions to the FDA under the "Animal Rule" amendment (21CFR parts 314 subpart I and 601 subpart H). The "Animal Rule" applies when adequate and well controlled clinical studies cannot be ethically conducted and field efficacy studies in humans are not feasible. At the end of the study, 29 of 43 rabbits were classified as Category E and 14 were classified as C.